Painful Hyperaesthesia Caused by Protease Inhibitors?

Introduction

The protease inhibitor ritonavir is known to cause peri-oral and peripheral paresthesias, usually immediately following intake of the medication [1]. With other protease inhibitors, so far no serious neurological disturbances have been described. Two patients treated with protease inhibitors (one patient with ritonavir, the other with indinavir) who developed very painful hyperaesthesia, are reported. Both patients had also used other drugs able to cause polyneuropathy, but the hyperaesthesia only decreased after the protease inhibitor was discontinued. During treatment with protease inhibitors, both patients developed polyneuropathy mainly characterized by paresthesias and hyperaesthesia very painful to touch of the distal parts of the lower limbs.

Case Report

Case 1: A 38-year-old homosexual man was diagnosed with HIV infection in 1995. His CD4 lmyphocyte count was 12/mm^3 at diagnosis. He was treated with zidovudine, zalcitabine and dapsone and was hospitalized several times due to fever, cough, and depression. No opportunistic infection was found. His condition improved during clarithromycin and ethambutol treatment. His viral load was 141,559 copies/ml plasma in August 1996. His clinical and immunological condition improved when ritonavir 600 mg b.i.d was added to his antiviral treatment. One month after the initiation of the ritonavir treatment, his CD4 count was 507/mm^3. His viral load had dropped to 230 copies/ml plasma. In the weeks following the start of the ritonavir, he developed oedema and a bluish-purplish discoloration of the feet. The veins of his feet and lower legs were congested. The patient complained of an extremely painful "pins and needles sensation" and hyperpathia to touch in the feet. These progressive sensory symptoms severely interfered with walking. The fingers were only mildly affected. Clinical neurological examination showed normal muscle strength and preserved tendon reflexes. Touch provoked very painful dysesthesias, but all other sensory modalities including pain, temperature, vibration sense and joint position sense were normal. The zalcitabine and dapsone were stopped, but the pain in his feet continued. Gait became impossible due to hyperpathia of the feet. Neurophysiological studies were refused by the patient. On the dorsal face of his right foot and the heel of his left foot, two bullous lesions appeared. These lesions were not caused by any obvious trauma. The fluid of the blisters was aspirated. Culture of the fluid did not reveal any pathogens. The lesions progressively disappeared after the blisters were aspirated. In September 1996, his CD4 lymphocyte count was 493/mm^3 and his viral load had decreased to under detectable levels. Ritonavir was replaced by indinavir 800 mg t.i.d., but the paresthesias and pain in his feet persisted. Therefore and despite the good virological and immunological response, the indinavir was stopped. In November 1996, the pain regressed but did not disappear. In March 1997, his CD4 lymphocyte count had dropped to 31/mm^3 and his viral load had increased to 511,200 copies/ml plasma. In Mai 1997, invirase 800 mg t.i.d. and lamivudine 150 mg b.i.d. was started. Since July 1997, he has been treated with invirase 600 mg t. i. d., nelfinavir 750 mg t.i.d. and lamivudine 150 mg b.i.d. The patient still complains of pain in his feet but the pain is bearable.

Case 2: A 35-year-old homosexual was diagnosed with HIV infection in 1989. He was treated for miliary tuberculosis and a tuberculous epididymitis in 1993. After completing his antituberculous treatment, he continued to take isoniazid 300 mg daily. Antiviral treatment with zidovudine 250 mg was started in August 1996. His CD4 count had decreased to 302/mm^3. The zidovudine was stopped and replaced by zalcitabine 1 month later because of an allergic reaction. In December 1996, stavudine 40 mg b.i.d. and lamivudine 150 mg b.i.d. were added. In January 1997, his CD4 lymphocyte count was 83/mm^3 and his viral load 1,707,692 copies/ml plasma. Indinavir 800 mg t.i.d. and dapsone 100 mg daily were started. Three weeks later, he developed pain in his feet. The pain increased during the following weeks and became particularly pronounced when standing. It made walking impossible. Touching his toes was very painful. It was impossible for the patient to put his feet in warm water because this was felt as boiling water. The veins of the lower legs were congested and his feet had a slightly bluish-purplish appearance. Muscle strength and tendon reflexes remained normal. Sensory and motor nerve conduction studies were normal with normal amplitudes of the motor and sensory evoked potentials. Concentric needle electromyography and tests of the autonomic nervous system were also normal. Sensory evoked potentials showed a normal conduction in the spinal cord and brain. In December 1996, lamivudine was stopped and in February 1997 zalcitabine treatment. Pyridoxine 250 mg once weekly was added to the isoniazid treatment. In March 1997, the CD4 lymphocyte count was 462/mm^3 and the viral load 472 copies/ml plasma. In March 1997, the stavudine and dapsone were stopped but the patient continued to complain of severe pain. In April 1997, the indinavir was halted. The pain in his feet, paraesthesia and hyperaesthesia regressed, but did not disappear completely. The indinavir was replaced by ritonavir 400 mg b.i.d. and saquinavir 400 mg b.i.d. In December 1997, he still complained of hyperaesthesia in his feet but was able to walk normally.

Discussion

These two case reports suggest that the protease inhibitors ritonavir and indinavir are able to cause a length-dependent sensory peripheral neuropathy characterized by very painful paresthesias and hyperaesthesia but with preservation of other sensory modalities on clinical examination. Neurophysiological examinations of the peripheral nervous system, the autonomic nervous system and the central sensory pathways were normal. These findings suggest an impairment of small diameter nerve fibres which are currently inaccessible to routine electrophysiological examinations.

Neither of these patients had a history of peripheral polyneuropathy before the start of protease inhibitors nor a history of chronic alcohol abuse or another predisposing condition except for HIV infection. The neurological symptoms and signs observed in the two patients differ from the "didanosine, zalcitabine or stavudine polyneuropathy," generally manifested as muscle weakness, decreased tendon reflexes and usually absence of or only

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mild hyperaesthesia [2, 3]. Symptoms of peripheral neuropathy caused by nucleoside analogues are generally reversible when drugs are stopped or given at a lower dose [2]. In the two patients described here, the symptoms of neuropathy did not disappear completely after the protease inhibitor intake was halted.
It is unclear whether the bullous lesions observed in case one were related to the ritonavir treatment. So far, we have never observed a similar phenomenon in any other patient treated with protease inhibitors. It is unclear whether the neurological complaints of the two patients were caused by the protease inhibitors alone or the combination of the protease inhibitors with other antivirals known to cause polyneuropathy, such as stavudine and zalcitabine or other drugs, such as isoniazid and dapsone. Certainly, patients receiving potentially neurotoxic drugs should be monitored carefully when treated with the protease inhibitors indinavir and ritonavir.

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References

1. **Markowitz, M., Saag, M., Powderly, W. G.:** A preliminary study of ritonavir, an inhibitor of HIV-1 protease, to treat HIV-1 infection. N. Engl. J. Med. 333 (1995) 1534–1539.
2. **Styrt, B. A., Piazza-Hepp, T. D., Chikami, G. K.:** Clinical toxicity of antiretroviral nucleoside analogues. Antiviral Res. 31 (1996) 121–135.
3. **Blum, A. S., Dal Pan, G. J., Feinberg, J.:** Low-dose zalcitabine-related toxic neuropathy: frequency, natural history, and risk factors. Neurology 46 (1996) 999–1003.

Book Review

W. G. Powderly (ed.)
Manual of HIV Therapeutics
254 pages, numerous illustrations and tables
Lippincott-Raven Publishers, Philadelphia 1997
Price: USD 40.–

This booklet is the result of an attempt to provide timely and relevant information on therapeutic knowledge about human immunodeficiency virus (HIV) infection and related complications from opportunistic diseases. It is not intended as a comprehensive reference and therefore discussions of pathophysiology and differential diagnosis are limited. The editor and authors have been only partially successful in meeting this goal.
This spiral manual is the work of 41 contributing authors, most of them staff members of the Washington University School of Medicine in St. Louis, Missouri and addressed primarily to practitioners caring for patients. However, it may also be useful for other health-care professionals as well as for medical students.
The first ten of 30 chapters cover the natural history of HIV infection, antiretroviral agents, antiretroviral therapy and therapeutic issues related to special patient situations: pediatric infection, women's issues, HIV in pregnant women and primary care and management of the terminally ill AIDS patient. The next eleven chapters are organized according to organ systems, while the remaining focus on classes of infectious agents, Kaposi's sarcoma, lymphoma and HIV-associated wasting.
All chapters are easy to read. Individual chapters are consistently structured into several sections and subsections which are headed by informative titles. There is no major overlap between organ system and pathogen-specific chapters. To avoid redundancy, the description of possible clinical presentations in the pathogen-specific chapters is minimal, while the organ-system chapters refer to specific pathogens for therapy.
The chapters vary in length and, to some extent, in quality. They range from five pages for a less frequently affected organ system, such as the cardiovascular system, to nine pages on ophthalmologic aspects. In the otherwise outstanding chapters on viral infections and mycobacterial disease, the number of references ranges from none to more than 50.
Most of the topics discussed in the chapters on opportunistic infections will probably remain relevant for years. This is certainly not the case for the chapter on antiretroviral therapy. With the most recent reference dating from 1995 and an unreferenced update in spring 1997, the chapter does not reflect current knowledge of this rapidly developing field. However, it provides a good basis for the understanding of more recent developments.

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